Patent Appl. No. 09/758,902
Docket No. PC9047D
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REMARKS

I. Preliminary Remarks

Claims 19 and 20 are under consideration. Upon entry of this paper, Claims 19 and 20 are currently amended. Claims 1-18 are cancelled. Support for the amendments to the claims is found throughout the specification, and in particular at paragraphs [0023], [0031], [0040] to [0046], [0056], and [0058], and Examples 1 and 2. The amendments do not include new matter.

In this response, Applicants address each of the rejections raised by the Examiner. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

This Response is filed with a petition to revive the application. The USPTO is given authorization to charge Deposit Account No. 16-1445 for any fees necessary with the submission of this Response.

II. Patentability Arguments

A. The Obviousness Rejection of the Claims under 35 U.S.C. §103(a) May Be Properly Withdrawn.

As stated in the MPEP (§2141), to support an obviousness rejection, four basic criteria must be met. These are (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and there must be some reason for making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. Clearly for prior art to render an invention obvious, it must render obvious the whole invention and not merely some part of the invention (*In re Antonie* 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1997)). The prior art must also be considered as a whole including parts that teach away from Applicant's invention. Applicant respectfully submits that these criteria are not met in the Examiner's rejections.

1. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seifert (Deutsche Tiearzliche Wochem. 90(7):274-279, 1983) in view of Geresi et al (Ann. Immunol. Hung. 25(0):37-40, 1985), Farmers and Consumers Market Bulletin (Department

of Agriculture, Atlanta, Georgia, 70(24): 1984, page 1, 12, ill.), and Kensil (US Patent 5,057,540 issued 1991). Applicants respectfully traverse this rejection.

The Examiner states that "Seifert teaches the use of a saponin adjuvant in the formulation of a multivalent clostridial vaccine using toxins of apparently different strains of Clostridial pathogens for the purposes of obtaining enhanced protective immune responses in a host. Seifert teach that the group has isolated three local pathogens from anaerobic infections and these pathogens are used for producing the anatoxin."

The vaccine composition of Seifert is entirely toxoid (inactivated toxin). Thus, there are no cells present. The cells are removed during filtration through the use of plasmapheresis hollow-fiber filtration (see the last two paragraphs of page 18, continuing on to page 19). Applicants' invention is to a *bacterin-toxoid* vaccine. This is supported in the specification (see paragraphs [0023], [0031], [0040] to [0046], [0056], and [0058], and Examples 1 and 2). The only components of the 8- or 7-way vaccines which are present only as toxoids are the *Clostridium perfringens* Type C and D (see paragraph [0056]). A vaccine comprising both bacterin and toxoid components would present more antigens to the subject and thus stimulate a broader serological response than one such as described in Seifert which contains only toxoids. Thus, Applicants' claimed invention is different than and non-obvious over the vaccine described in Seifert.

Seifert does not exemplify a multicomponent clostridial bacterin and toxoid vaccine with saponin as the sole plant-derived adjuvant. In addition, Seifert utterly fails to establish that any of the "*Clostridial*" components present in its vaccine were responsible for the observed protection. All of the assertions made in Seifert with respect to the effect of a vaccine are based on the results of virtually uncontrolled vaccinations and on observations without scientific analysis. Seifert (page 12, lines 12 to 15) states: "it must be pointed out that it is difficult to conclude from the field reports whether any deaths are to be attributed to anthrax or to gas gangrene. Unfortunately, it is not possible to obtain sufficient sample material to check this." (emphasis added) (see also page 6, lines 7-8; page 8, lines 11-12; and page 12, first paragraph)

Seifert does not provide the cause of death with certainty, or even the specific cause of the disease complex. Thus, Seifert cannot provide an analysis to explain the results of the

vaccinations. There is no analysis of the immune response of the vaccinated animals. There is no indication of which components of the vaccine contributed to the observed drop in mortality. Indeed, Seifert states (page 6, lines 7-11) "As a reservation, it must be said, in relation to these general remarks, that it is in many cases not clear whether the cause of death is an anaerobic infection or anthrax. In association with our own laboratory investigations in Madagascar, it was found that at most 5% of the deaths identified as being anaerobic infections are in fact such infections; in most cases, the deaths are in fact due to anthrax." Thus, the anthrax spores alone may have provided the entire benefit of Seifert's vaccine.

Seifert even fails to establish that the vaccine comprises toxiods from multiple Clostridial species because it fails to establish that all of the three purportedly "clostridial" strains of bacteria used to prepare the toxoids for the vaccine composition taught therein are, in fact, members of the genus *Clostridium*.

Seifert does state (page 5, lines 13-14) that strain No. 735 was identified as *C. chauvoei*. By contrast, Seifert states (page 11, lines 17-19) that strain No. 335 grows anaerobically "with all the culture characteristics of a gas edema pathogen; but with the help of gas chromatography, it can be definitely separated from all conventional *Clostridia* of the gas edema group." (emphasis added) Thus, Seifert does not positively identify strain No. 335 as an actual *Clostridium*.

Seifert states (page 11, lines 19-23) that "While strain 217 resembles the perfringens group in its bacteriological characteristics this is not the case with regards to its biochemical characteristics. This pathogen can also be distinguished by gas chromatography from the classical gas gangrene pathogens owing to the fatty acid pattern which it forms." (emphasis added) Thus, Seifert states that strain No. 217 is different from all conventional *Clostridia* of the gas edema group; Seifert does not positively identify strain No. 217 as an actual Clostridium.

In summary, Applicants' invention is not obvious over Seifert because Seifert 1) teaches a vaccine composition comprising clostridial toxoids and not clostridial toxoids and bacterins; 2) fails to establish the precise nature of the disease being treated; 3) fails to establish that all three strains of bacteria used to produce the toxoids used in the vaccine composition are, in fact, members of the genus *Clostridium*; 4) teaches a vaccine

composition comprising *B. anthracis* (anthrax) spores; and 5) fails to determine whether the clostridial components of the vaccine contributed to the observed drop in mortality. Seifert et al. do not teach or suggest that a multicomponent clostridial bacterin and toxoid vaccine composition formulated with saponin as the sole plant-derived adjuvant but lacking immunogens from *B. anthracis* would be effective against clostridial infection. Thus, Applicants submit that Seifert does not render the instant claimed invention obvious.

The Examiner also states that "It would have been prima facie obvious to one having ordinary skill in the art at the time that the invention was made to modify the Seifert vaccine by adding any desired additional clostridial components as taught by Geresi or Farmers and Consumers Market Bulletin and include a respiratory viral antigen as taught by Farmers and Consumers Market Bulletin because Geresi and Farmers and Consumers Market Bulletin teach that it is conventional to combine the multivalent clostridial vaccine with viral components and both Seifert and Kensil teach the use of saponin as an effective adjuvant for the enhancement of an immune response with either a clostridial or viral antigen respectively the combined vaccine would provide the advantage of reduced time and cost for administering multiple vaccines to farm/ranch animals."

However, Applicants submit that the multiple deficiencies of Seifert are not cured by any of the secondary references. The cited references, either alone or in combination, do not teach or suggest Applicants' invention, as presently claimed.

Geresi et al. teach a freeze-dried vaccine composition having *C. perfringens* toxins and another combined antigen. Geresi do not teach the use of clostridial bacterins, as used in Applicants' invention. In addition, Geresi teach that the combination of *C. perfringens* antigens "depressed the value of the immunity-degree developed after the introduction of the combined antigens." (see page 39; paragraph (i)) Thus, Geresi disclose that antigen competition results in a reduction in the immunity conferred by the vaccine. Geresi also fails to teach the use of an adjuvant. Geresi do not make up for the deficiencies of the Seifert reference and actually teaches away from Applicants' invention. One skilled in the art would not combine Seifert and Geresi.

The Examiner states that one having ordinary skill in the art at the time that the invention was made to modify the Seifert vaccine by adding any desired additional clostridial

components as taught by Farmers and Consumers Market Bulletin and include a respiratory viral antigen as taught by Farmers and Consumers Market Bulletin. However, adding the viral antigens of Farmers and Consumers Market Bulletin to the Seifert vaccine does not make up for the deficiencies of Seifert as discussed above.

Kensil et al. teach a method to fractionate a mixture of saponins extracted from *Quillaja saponaria* and test the adjuvant effect of the individual fractions in mice using either bovine serum albumin (BSA) or gp70R-delta as the antigen. Kensil do not teach or suggest the use of saponin as an adjuvant for use in a clostridial vaccine. Applicants respectfully submit that BSA does not have the problems of low antigenicity and poor stability, which are associated with clostridial antigens. In this reference, the gp70R-delta was absorbed to aluminum hydroxide, which has an adjuvant activity for many proteins. Understanding the effect of saponin as an adjuvant with a virus is confounded by the addition of aluminum hydroxide. Therefore, those skilled in the art would not have readily extrapolated the results of Kensil to clostridial antigens. In other words, Applicants respectfully submit that those skilled in the art would not have gained a reasonable expectation of success in arriving at the claimed invention based on Kensil. Thus, Kensil teach only that saponin can function as an adjuvant for a single-component, nonclostridial antigen. Kensil do not teach that saponin would be an effective adjuvant for a complex antigenic mixture such as that found in a multi-component clostridial vaccine. Applicants submit that Kensil, either alone or in combination with Seifert, would not have taught or suggested to a person skilled in the art the use of a rapidly dispersed adjuvant such as saponin in multi-component clostridial vaccines.

Seifert does not teach or suggest Applicants' invention. The combination of Seifert and the other cited references also does not teach or suggest Applicants' invention. Accordingly, it is respectfully submitted that Claim 20 is not rendered unpatentable over Seifert in view of Geresi, Farmers and Consumers Market Bulletin, and Kensil. Thus, based on the remarks presented herein, the rejection of Claim 20 under 35 U.S.C. §103(a) is overcome. Withdrawal of the rejection is respectfully requested.

2. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seifert (Deutsche Tiearzliche Wochem. 90(7):274-279, 1983), Geresi et al (Ann. Immunol. Hung. 25(0):37-40, 1985), Farmers and Consumers Market Bulletin (Department of Agriculture,

Atlanta, Georgia, 70(24): 1984, page 1, 12, ill.), and Kensil (US Patent 5,057,540 issued 1991) as applied to claim 20 above further in view of Green et al (The Veterinary Record, 120:435-439, 1987). Applicants respectfully traverse this rejection.

The Examiner states that the teachings of Seifert, Geresi, Farmers and Consumers Market Bulletin are combined as set forth above. In addition, "Green et al teach the formulation of a multi-valent clostridial vaccine for the purposes of stimulating a protective immune response against multiple serotypes and species of this pathogen. Green et al teach three known commercially available vaccines comprising at least 7 different serotypes/species of Clostridium for protection from infection (Tasvax, Heptavac, Covexin) page 435, column 2, Table 1. It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the composition as combined *supra* by adding the other known individual clostridial vaccine toxoid components of Green et al (i.e. *C. perfringens* (serotype D), *C. septicum*, *C. novi*, *C. haemolyticum* and *C. chauveoi*) because combined vaccines were commercially available and known to be effective for broad protection for a variety of pathogens in farm animals."

Green et al. fail to teach a viral antigen in the multivalent clostridial vaccine. Green teach a vaccine composition that includes an aluminum hydroxide adjuvant, while Applicants' claimed invention is to a vaccine composition comprising a saponin. Green fail to teach the use of a rapidly dispersed adjuvant, *e.g.*, saponin, in a multicomponent clostridial vaccine.

As submitted above, the Seifert reference does not provide adequate teaching for an effective bacterin and toxoid vaccine that protects vaccinated animals from virulent Clostridium pathogens. Furthermore, the Seifert reference does not clearly teach that the use of saponin as the sole plant-derived adjuvant would be effective for clostridial antigens. Applicants further respectfully submit that the cited secondary references, including Green et al. do not cure the deficiencies of the Seifert reference. Therefore, the cited references, either alone or in combination, do not teach or suggest a multicomponent clostridial bacterin and toxoid vaccine composition formulated with saponin as the sole plant-derived adjuvant, as presently claimed. Accordingly, it is respectfully submitted that Claim 19 is not rendered unpatentable over Seifert in view of Geresi, Farmers and Consumers Market Bulletin, Kensil,

and Green. Thus, based on the remarks presented herein, the rejection of Claim 19 under 35 U.S.C. §103(a) is overcome. Withdrawal of the rejection is respectfully requested.

III. Conclusion.

In view of the amendments and remarks made herein, Applicants respectfully submit that Claims 19-20 are in condition for allowance and request expedited notification of same.

Respectfully submitted,

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